National Institute of Allergy and Infectious Diseases

NIAID

# Council News

*June 1998 Council* *Vol. 7 No. 2*



## NIH Budget Wends Its Way Through Congress

**Through a new 21st Century Research Fund, President Clinton wants to increase the NIH budget by $1.15 billion, more than 50 percent, during the next five years.**

The President's FY 1999 budget requests an 8.6 percent hike for NIAID, bringing the level to $1.47 billion; NIH's budget goes up 8.4 percent to $14.79 billion under the request.

NIAID director Dr. Anthony S. Fauci told Council "how pleased we are that the Clinton Administration has shown such a commitment to biomedical research."

Nevertheless, the fate of the new monies is still unclear. Most hinge on a tobacco settlement, and the President will likely veto the House budget bill, putting the government under a continuing resolution this fall.

In March and April, Dr. Fauci testified before the House and Senate appropriations subcommittees. Both chambers of Congress continue to be very "supportive of our efforts," he told Council.

Dr. Fauci also said that Congress showed "an extraordinary interest in global health, particularly diseases like malaria and others that have a strong public health and economic impact in other countries."

Global health was brought to the forefront as a national goal by a task force on NIH priority-setting led by Congressman George Nethercutt of Washington last year.

Other areas of congressional interest are bioterrorism, asthma, H5N1 flu, diabetes, hepatitis C, antibiotic resistance, pathogen genome sequencing, and AIDS, including the timeline for an AIDS vaccine.

Dr. Fauci also said that NIH director Dr. Harold Varmus moved $4.5 million of his discretionary fund to NIAID for tolerance research.

## *Inside*

*INITIATIVES & funding*

# NIAID Will Award Some SBIR Grants as Much as $3.6 Million

**In May, NIAID launched a new program to make Small Business Innovation Research (SBIR) more attractive to biomedical investigators.**

Called SBIR-AT-NIAID (AT stands for Advanced Technology), the program gives phase I applicants up to $300,000 a year and phase II awardees up to $1 million a year.

SBIR-AT-NIAID puts a twist on the traditional phase I to phase II structure. It stretches the exploratory phase I from six months to two years, and the phase II development award, from two to three years (provided that funding is approved).

Phase II applications can be continuations of ***any*** NIH phase I SBIR award (i.e., they are not required to have been an SBIR-AT-NIAID award).

Following NIH policy, applicants requesting more than $500,000 must contact NIAID program staff as they develop plans ***and*** get written agreement from NIAID that the application will be considered for an award.

To read more, see the full program announcement at **http://www.nih.gov/grants/guide/pa-files/PAR-98-073.html**.

For more information on the SBIR-AT-NIAID program and other SBIR issues, contact:

*Mr. Vincent Thomas*

*Telephone: 301/496-7291*

*E-mail: vt5e@nih.gov*

## Features of SBIR-AT-NIAID

### Phase I

Awards up to two years; not to exceed $300,000 a year total cost.

Consultant and contractual costs up to 33 percent for clinical studies in academic institutions.

Applicants can request an extension of the 25-page limit.

### Phase II

Awards up to three years with funds not to exceed $1 million per year total cost.

Consultant and contractual costs up to 50 percent for clinical trials.

### General

Receipt dates April 15, August 15, and December 15.

## SBIR-AT-NIAID PA research areas

Develop vaccines, biologics, drugs, and preventions for infectious and immunologic diseases, allergy, and transplantation.

Develop assays, reagents, or services for clinical and vaccine trials.

Apply nanotechnologies, including DNA chips, protein-protein interaction chips, and others.

Create bioinformatics programs and databases to analyze data generated from chip technologies.

Use high-resolution imaging to localize and monitor *in vivo* immune cells, pathogens, and disease progression or remission.

Develop reagents to identify antigen-specific T cells to track and characterize immune responses.

Develop and evaluate topical microbicides.

Develop and evaluate methods to control vector-borne infections.

# Balancing the Budget to Keep a Healthy Stream of Research Funding, Why Paylines Are Not Key

**NIH and NIAID are grappling with the prospect of a budget increase. While obviously a positive move, fiscal choices will have to be made, and expectations may exceed budget realities.**

NIAID has been in excellent fiscal health during the past three years.

We are funding more investigators than ever before, and more applicants have been successful relative to those applying for grants.

Numbers of competing (new or recompeting) grants grew almost 40 percent—from 426 to 591—from FY 1996 to FY 1998 alone (see the graph on the next page).

While this success is positive, it has greatly expanded NIAID's commitment base (the money the Institute spends on all years of a grant; most of the base is fixed due to the multiyear nature of NIH grants, which average four years in length).

Obviously, the larger the base, the less money is left in the budget for new awards.

Thus, the current growth rate will probably not be sustainable, even though grant numbers will continue to rise in FY 1999.

Next fiscal year, NIAID will have to strike a balance between the need to maintain its commitments and keep enough monies free to fund a healthy number of new awards.

Burgeoning numbers of grants and high-quality applications (with fundable percentiles), therefore, will likely prompt the Institute to lower its payline in FY 1999.

Though NIAID's final budget is not known, we are projecting an FY 1999 payline around the 20.0 percentile. (FY 1998 paylines were at the 24.0 percentile for non-AIDS and 26.0 for AIDS-related applications.)

## *What is the payline?*

The payline is the projected cutoff point, set at the beginning of the fiscal year, within which most grants are funded.

So an application with a percentile rating of 19.0 will get an award if NIAID's payline is at 20.0, but a grant with a percentile of 21.0 will not.

This appears to be straightforward but in fact is rather complex.

Programmatically important grants, some applications responding to program announcements, applications responding to RFAs, contracts, bridge awards, and training grants are funded from separate budget categories and therefore do not affect the R01 payline.

Further, the payline is just an estimate. NIAID cannot know ahead of time how all the budgetary factors will play themselves out during the year, so the payline tends to be conservative (thus, at the end of the fiscal year, an additional number of grants with higher [worse] percentile rankings often get paid).

## *How important is the payline?*

Investigators often look at an institute's payline to judge how advantageous it would be to target an application there.

***Due to the expansion of our budget's commitment base, the current growth rate may not be sustainable***

When NIAID's payline was lower than it is today, some applicants requested assignment to other institutes.

Now the tide has turned. More people are requesting to have their grants assigned to us; and our program announcements are attracting strong numbers of new applications.

As we stated above, these factors will likely require NIAID to pull paylines back somewhat from FY 1998 levels.

The question for researchers is, what's the impact on me?

Though there may be a slight drop in the numbers of grants we fund, total grant numbers will continue to be strong.

These are better measures of how advantageous it is to apply to NIAID than is the payline, primarily for the reasons stated above and because paylines do not reveal how many people are getting grants relative to those who are trying.

## *Budget forces have an impact*

Other competing forces are also affecting the budget.

The average cost of a grant is going up. Modular grants (see article on page 5) will have an impact due to rounding up of dollar levels, and NIAID is funding more expensive grants, especially those for pathogen genome sequencing (which are two to four times as costly as the average R01).

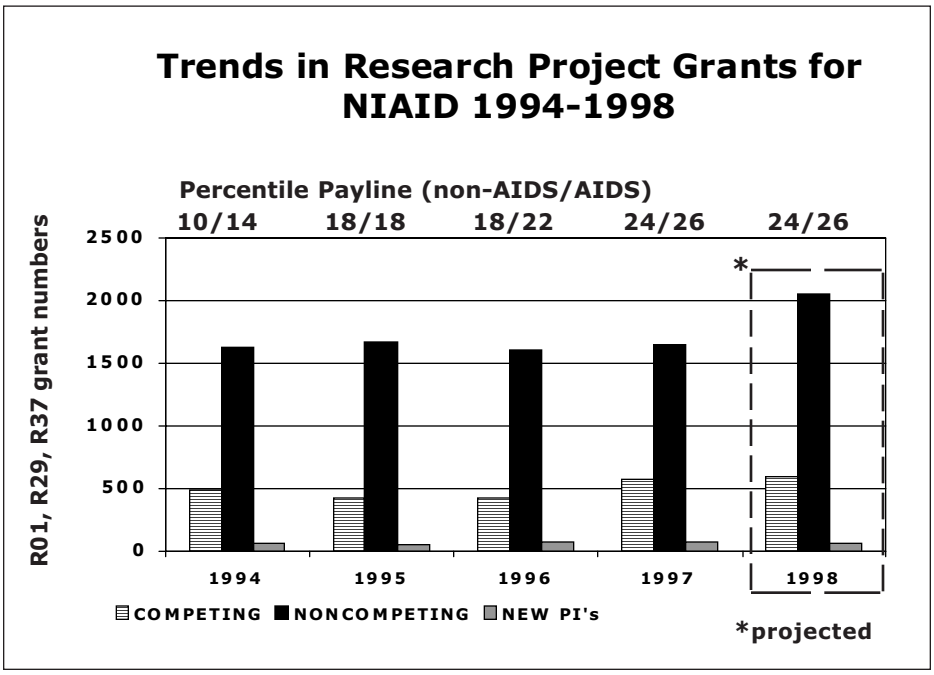
While these items pull on the purse strings, so do investigators' high expectations that institutes will deliver a range of requests. These include:

- Elimination of PI salary caps.
- Reductions to budgetary (programmatic) grant adjustments.
- The transition of new investigators from R29 to higher dollar R01 awards.
- The desire for new high-tech research resources, including imaging and microchips.

Further, NIAID's budget is tapped by various sources at NIH and the Department of Health and Human Services for a range of purposes.

Altogether, the latest budgetary factors portend lower paylines, bucking the trend of the past several years.

Nevertheless, investigators should keep in mind that NIAID will still be funding a large number of new grants next fiscal year.




# NIAID Cosponsors Hepatitis C RFA

**Seven NIH components, including NIAID, and the American Digestive Health Foundation are sponsoring a request for applications (RFA) to stimulate basic and clinical research to counter the growing threat of hepatitis C.**

The RFA covers a broad range of research areas, including epidemiology, vaccine and drug development, natural history, pathogenesis, transmission, model systems, and more. For more information, see the announcement in the *NIH Guide* at **http://www.nih. gov/grants/guide/rfa-files/RFA-DK-98-017.html**, or please contact:

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*NIH news*

## Modular Grants Get the Green Light

**By winter, NIH expects to be awarding modular research grants, helping to cut back on budget processing and ultimately end programmatic reductions to grant budgets.**

For the first modular grants, budgets will be awarded in increments of $25,000 to a maximum of $250,000. Instead of requesting detailed, categorical budgets, applicants will request direct costs in the $25,000 modules. NIH will use the modular approach for most research project grants.

Modular grants simplify budget requests, taking NIH out of the role of verifying costs and practices. For example, grantees will continue to identify personnel but will not send in salary and fringe benefit costs.

Annual inflationary adjustments will be gone, though grantees can ask for additional modules if there are programmatic changes.

NIH institutes are not bound to use the $25,000 increment when determining award levels and will still be able to negotiate awards for less money than the amount recommended by the study section or Council.

The move toward modular was endorsed by independent auditors Ernst and Young as moving NIH into more of an assistance

**Modular Grants**—*continued on page 20*

## PAs Older Than Three Years to Retire

**NIH is adopting new policies on expiring program announcements.**

First, all future PAs will stay alive for three years (unless the announcement states otherwise).

Second, all PAs older than three years will be terminated. Institutes wishing to keep older PAs active will issue new ones.

NIAID has only two active PAs more than three years old and is deciding whether to reissue them. Any such changes will be announced in the NIH *Guide for Grants and Contracts* around the time this newsletter is published.

## Apply for a Reentry Supplement

**People coming back to research after a hiatus can apply for a reentry supplement, money that lets the recipient tag on to an existing (i.e., someone else's) grant.**

Applicants can request $40,000 a year for salary and benefits and another $10,000 for travel for three years. For more information, see the announcement at **http://www.nih.gov/grants/guide/notice-files/not98-079.html** in the June 4 *Guide*.

In the past, NIAID has awarded grant supplements for a range of people, including those with disabilities, minorities, and people returning to work from family responsibilities. Historically, supplements have been fairly easy to get, and the program is user-friendly, with minimal paper work.

***Historically, supplements have been fairly easy to get, and the program is user-friendly***

Call your program officer for more information; go to our programs and staff list at **http://www.niaid.nih.gov/ncn/newsup.pdf**, or e-mail Dr. Milton Hernandez, acting director of the Office of Research on Minority and Women's Health, at nh35c@nih.gov, or call him at 301/496-8697.

# IOM Advises NIH to Improve Input When Setting Priorities

**An Institute of Medicine report released on July 9 advises NIH to do a better job of involving the public when determining its research priorities. Spurred by concerns from advocacy groups and Congress about how NIH allocates funds to different diseases, the committee determined that the process NIH uses to define priorities has served the nation well but could be strengthened.**

Though NIH's criteria for setting priorities are sound, decision making would be improved and better accepted by giving the public more say in the process, which would also help NIH's public relations.

***The committee felt that NIH decision making would be improved and better accepted by giving the public more say in the process***

The committee had two suggestions to build a structure for public input.

First, it advised creating public liaison offices in each institute and a central liaison office.

Second, the committee recommended establishing a council of public representatives that advises the NIH director. Plans to implement these suggestions are under development.

Other recommendations may also have an impact.

To improve public awareness of how priorities are made and resources allocated, NIH should do a better job of analyzing and using health data on the burden of different diseases.

Further, the NIH director should require strategic plans from all institutes to ensure a uniform approach.

## NIAID cited for its planning process

Like other institutes, NIAID provided information to the committee and was ultimately cited by it for our comprehensive planning process.

The committee noted that to review its priorities, NIAID has two annual retreats and other efforts that include representatives of the scientific community in planning (see box on the next page).

During the past few years, NIAID has bolstered its efforts to solicit input by holding focus group meetings with the extramural research community and by including patient advocates in some review meetings for clinical applications.

## Setting NIH research priorities

The committee identified five criteria NIH uses to determine priorities:

- public health needs
- scientific quality of the research
- potential for scientific progress
- portfolio diversification along expanding frontiers of science
- adequate support of infrastructure

According to the report, NIH has a two-part mission: 1) identify public health needs and reduce disease burden and 2) extend the base of basic knowledge.

These two concepts may be closer to each other than many scientists believe.

See the article on page 8 for a perspective that juxtaposes science and agency objectives.

Produced by the Committee on the NIH Research Priority-Setting Process, the congressionally mandated report is called "Scientific Opportunities and Public Needs: Improving Priority-Setting and Public Input at the National Institutes of Health."

Find it on the Web at **http://www.nap.edu/readingroom/books/nih**, or you can order a printed copy by calling 1-800/624-6242.

## Priority-Setting at NIAID

The NIAID planning process is organized around two major, Institute-wide planning meetings that engage the Institute director, scientific program heads, and senior management staff in a collective effort to identify and establish priorities for future research.

The process is designed in sequence with the federal budget formulation and is thus focused two years into the future.

The first step is the Summer Policy Retreat, which provides a forum for planning future scientific directions. Discussions from this retreat are then transmitted to the NIAID advisory Council for feedback and input.

A Winter Program Review is then convened to consider the deliberations that preceded it and define current gaps in knowledge, emerging public health needs, and research opportunities.

Following the Winter Program Review, NIAID Divisions submit their proposed initiatives to the budget office. The Institute director, in consultation with senior management, then selects the initiatives that will become part of the budget submission to the NIH director. These plans are also submitted to the NIAID advisory Council for review.

Throughout the process, the Institute director and the Division directors meet with national organizations, voluntary health organizations, and professional societies. Focus groups are convened at scientific and professional society meetings to receive further input. Input from patient groups occurs at the community level through patient participation on local and national advisory boards that provide advice to large clinical trials networks.

# NIH's Center for Scientific Review Adopts New Scoring for Grant Applications

**Beginning in June, reviewers started assigning priority scores between 1.0 and 3.0 to the top half of applications and between 1.0 and 2.0 to the top quarter.**

CSR made this move to help spread scores for the best applications, better enabling NIH to discriminate among them.

The change adds another dimension to scoring by increasing the importance of an application's rank relative to others reviewed by the study section.

We will be closely monitoring the impact during the next year.

Introducing a new scoring system requires NIH to base percentiles for June on that review only as opposed to its usual practice of using three review meetings as the basis for calculating the rankings. NIH will be phasing in its return to the three-meeting norm.

The Center for Scientific Review published a notice in June on this subject. It's on the Web at **http://www.drg.nih.gov/review/scoring.htm**.

# Weaving Together the NIH Mission and Your Science Interests

**Understanding how basic science and applied research feed each other may hold the key to fusing your research interests with NIH's drive to fulfill its mission. Study sections have been slow to recognize the value of research that leans toward the applied, favoring pure basic research applications.**

But this may be changing, as is evidenced by such changes as the creation of the new NIH vaccine study section (see the article on page 10), heightening credibility for research beyond basic immunology and other topics not geared toward vaccine development.

The central NIH mission is to improve public health.

**Research Paradigm Linear Continuum**


Viewing research as progressing in linear fashion from basic to applied does not adequately define areas of transition between basic research and studies leaning toward applications that achieve those ends.

Further, a linear model may simply be wrong.

Speaking at BIO 98 (see the article on page 11), Dr. John McGowan, director of NIAID's Division of Extramural Activities, suggested that the interplay between basic research and applied research is not adequately portrayed by the linear model.

For example, basic research led to the development of new tools, such as polymerase chain reaction and microchip technology, that in turn spawned new avenues of basic research.

## *Basic and applied research feed each other*

A more dynamic paradigm builds a better framework for conceptualizing the interplay between basic and more applied research that primes the research enterprise.

This is very different from the linear model, which presumes that basic research gives no thought to practical ends.

Basic research does not exist in a vacuum—technology inspires research as often as the other way around, and both build the knowledge base. The heart of NIH research, the R01 grant, floats in a fluid gray zone between the blurred edges of pure basic and more applied, or "use-inspired," research.

Showing a link between research and conquering public health threats is especially salient for funding authorities; NIH alone spends more than $10 billion a year of the tax payers' money on biomedical research.

When planning their research projects, therefore, Dr. McGowan advised scientists to think in terms of how their work fits into a larger framework. Investigators who understand the NIH mission will benefit from this perspective when seeking partnerships and funding.

## *PCR as an example*

PCR technology illustrates the give-and-take between basic and applied research. Basic government-sponsored research of bacteria living near thermal vents on the ocean floor revealed heat-stable enzymes that can amplify tiny amounts of

DNA. These extraordinarily useful reagents revolutionized biomedical research, spawning a host of new basic discoveries, some of which progressed to practical applications.

New nanotechnologies, such as microchips, will likely be the next triggers to explode basic biomedical knowledge.

In the book *Pasteur's Quadrant,* author Donald Stokes makes the case for this scenario. He portrays NIH as a model government agency for melding pure basic research with topics that address societal needs.

Published by the Brookings Institute, *Pasteur's Quadrant* credits NIH with successfully following a path carved out by Louis Pasteur, built on a vibrant interchange between basic research and the needs for knowledge that drive it.

Pasteur's model is fashioned around the concept of use-inspired research, a continuing cross-fertilization between basic and applied areas (see graphic below).

Research can be sectored into four quadrants: pure basic, use-inspired, pure applied, and a fourth, which is driven by neither knowledge nor application but interest in a given topic (see graphic at top of page).

Pasteur earns the title to the use-inspired quadrant because of his success in applying basic research to achieve practical ends.

*Pasteur's Quadrant* cited NIH as the federal agency with the best model for generating use-inspired research through its broad range of support of research projects spanning the range from very basic to applied.

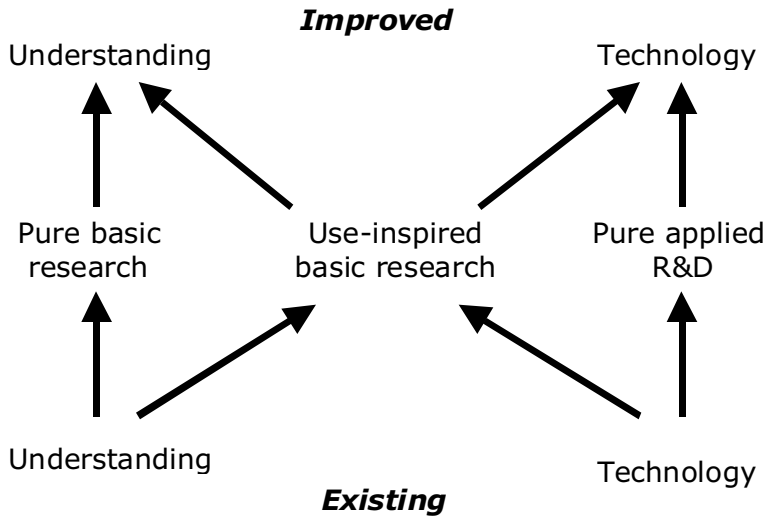
| **Research is inspired by:** | **Considerations of use?** No | **Considerations of use?** Yes |
|---|---|---|
| **Quest for fundamental understanding?** Yes | Pure basic research<br>*Bohr's Quadrant* | Use-inspired research<br>*Pasteur's Quadrant* |
| **Quest for fundamental understanding?** No | (Activity in pursuit of neither knowledge nor application) | Pure applied research<br>*Edison's Quadrant* |

## Following in Pasteur's footsteps

Though the use-inspired paradigm is not widely used by biomedical scientists, it, in fact, underlies how NIH funds research.

NIH is moving toward recognizing the importance of use-inspired research, by creating new applied research study sections and through its bioengineering initiative, which bolsters exchanges between scientists and engineers. Nevertheless, the debate on where to draw the line between funding basic versus applied research will surely persist and will do so to the benefit of both NIH and the research community.

**Dynamic Model of Research**




**NIH News**—*continued on page 19*

*VACCINE focus*

# CSR Readies New Vaccine Study Section

**Vaccine research should reap the benefits of a new initial review group geared especially to studies that use basic research information to understand how to develop a vaccine, work that lacked a study section targeted specifically to it.**

Responding to concerns of the research community, NIH's Center for Scientific Review (CSR) set up an initial review group to review applied vaccine research for HIV and other pathogens. (Basic, early vaccine-related research and design will continue to be reviewed in AIDS and microbiology study sections.)

Recruitment for the new study section is already under way. The first applications were referred to it in June; the first AIDS applications will come in for the September 1 receipt date. Applicants are strongly encouraged to self-refer.

**Send comments to**

*CSR: Maryclare Walker*
***mw31y@nih.gov***

*DAIDS: Polly Sager*
***ps31g@nih.gov***

*DAIT: Charles Hackett*
***ch187q@nih.gov***

*DMID: Regina Rabinovich*
***rr28k@nih.gov***

Infectious disease vaccinology cuts across vaccine development areas, including:

- vaccine delivery approaches
- methods to assess immune responses
- assessment of safety, reactogenicity, toxicity, and immunogenicity in animals and people
- efficacy studies in animal models

Scientific merit will be assessed by a core 10- to 15-member committee, which will rotate reviewers depending on the expertise needed for the applications at hand.

Areas of expertise include pathogenesis of viruses, bacteria, and protozoa; pathogen immunology; animal models; vectors; adjuvants; cytokines; vaccine delivery; vaccine production; statistics; and modeling.

NIH is soliciting comments about the new study section from the community (see contacts in the insert at left). For more information go to **http://www.drg.nih.gov/review/vaccine.htm**.

# Intramural Scientists Develop DNA Vaccine for Rabies

**A DNA vaccine protected eight monkeys from a lethal dose of rabies virus. Developed by researchers at NIAID's Rocky Mountain Laboratories, it is the first DNA vaccine to completely protect primates against a virus in the central nervous system.**

Though few Americans die of the disease because of the use of post-exposure prophylaxis here, thousands die worldwide in countries where such measures are not readily available. In the recent studies, vaccinated monkeys received two doses about 190 days apart before challenge with DNA that encodes the surface glycoprotein of the virus.

Investigators are working to overcome the drawback of the approach: the antibody response took 30 days to occur.

This work was published in *Nature Medicine*, 1998;4(8):949-52.

## Ushering in an Era: Edible Vaccines

**An edible vaccine triggers good immune responses against *Escherichia coli*, reported collaborating scientists from the University of Maryland, Boyce Thompson Institute for Plant Research, and Tulane University—all supported by NIAID.**

Edible vaccines open an exciting new potential to prevent global scourges such as hepatitis and diarrhea.

Vaccine-housing crops can be grown locally, circumventing problems of storage and administration that plague the use of traditional vaccines in the less developed world.

In addition to pathogenic *E. coli*, a major cause of diarrhea worldwide, scientists are already exploring the technique for other antigens.

Edible vaccines are in early development for other intestinal pathogens: potatoes and bananas for Norwalk virus, potatoes and tomatoes for hepatitis B.

The phase I *E. coli* trial began last fall at the University of Maryland School of Medicine's Center for Vaccine Development under the direction of Carol Tacket, M.D.

Volunteers ate bite-sized pieces of raw potato genetically engineered to produce part of an *E. coli* toxin.

Just before being eaten, the potatoes were peeled and cut into 50-gram and 100-gram doses. Each participant received three doses of either 50 grams or 100 grams of potato over a three-week period.

Ten of the 11 volunteers had fourfold rises in serum antibodies, and six had fourfold rises in intestinal antibodies. No serious adverse side effects were reported. Earlier *in vitro* and preclinical studies by John Clements, Ph.D., and colleagues at Tulane University School of Medicine showed that transgenic potatoes with the same toxin segment stimulated strong immune responses in animals.

The transgenic potatoes were created and grown by Charles Arntzen, Ph.D., Hugh S., Mason, Ph.D., and colleagues at the Boyce Thompson Institute for Plant Research, an affiliate of Cornell University.

***Edible vaccines are in early development for intestinal pathogens: potatoes and bananas for Norwalk virus, potatoes and tomatoes for hepatitis B***

The study was reported in May *Nature Medicine* (vaccine supplement), 1998;4(5): 502-03 Haq TA, Mason HS, Clements JD, and Arntzen CJ.

## NIAID Cosponsors Vaccine Symposium—Medicine for the 21st Century

**NIH is looking to partner with industry to spur research of new vaccines.**

On June 15, NIAID cosponsored a symposium at BIO 98 to bridge interest in vaccine development with the biotech community and industry. Called Vaccines: Visions for the Future, the symposium ventured into the waters of vaccine high technology, some of which are flowing into such mundane channels as bananas and milk.

Companies are well into the development of new vaccine technologies including edible, DNA, and aerosol vaccines; transgenic milk; genomics; and plant factories as well as vaccines for an expanded list of difficult organisms, including TB, meningococcus, rotavirus, and malaria.

First of the new-generation vaccines is a live-attenuated, cold-adapted, trivalent influenza nasal spray vaccine for flu.

**Vaccine Meeting**—*continued on page 19*

# Panel on Vaccine Immunology Defines Needs in the Field

**On June 9, NIAID's Division of Allergy, Immunology, and Transplantation invited an expert panel of vaccine specialists to confront a major issue for vaccine development.**

Natural immune responses fail to clear the initial infection or provide long-term protection for a growing number of killer diseases, including tuberculosis, malaria, hepatitis C, and HIV.

To produce a vaccine that breaks through the natural barrier, scientists need to understand host-pathogen interactions and the limits and capabilities of the immune response.

The panel of basic, clinical, and industry vaccine scientists emphasized the importance of basic immunology in tackling such issues.

They recommended funding more basic immunology research relevant to vaccines and more involvement of basic immunologists in the vaccine field.

Basic immunologists and clinical investigators play complementary roles in studying human innate and adaptive immunity and host-pathogen interactions.

Questions concerning the immunobiology of the host response are perhaps the most difficult to answer in vaccine research today.

For insights into basic vaccine responses, immunologists would do well to look for new information from other disciplines, e.g., microbial genetics and pathogenesis, as well as data and materials from clinical studies.

## Participants

Rafi Ahmed
Jack Bennink
Martin Bryant
Gail Cassell
Mary Lou Clements-Mann
Francis Ennis
Clifford Harding
Charles Janeway
Marc Jenkins
Arthur Krieg
Thomas Monath
Yvonne Paterson
Steven Porcelli
Kenneth Rock
Robert Siliciano
Jonathan Yewdell

## Key discussion points

Increase study of uniquely human features of immune responses.

Heighten understanding of the host-pathogen interface.

Limit boundaries between disciplines and encourage collaborations between basic immunologists, clinicians, microbiologists, and industry vaccine researchers.

Develop integrated programs for new vaccine approaches based on advances in basic immunology and insights from clinical studies.

# New Flu Sequence Web Site

**With more than 4,000 nucleotide and amino acid sequences, the new Influenza Sequence Database is a valuable resource for depositing and querying sequence information.**

Produced by the Los Alamos National Laboratory, it now houses influenza A sequences, and more are slated to be added.

You can find the database on the Internet at **http://www-flu.lanl.gov/index.html**.

*INSTITUTE & staff*

# New on the Internet: a Database of Compounds Screened for Anti-HIV Activity

**NIAID's Division of AIDS has begun uploading a vast drug development database on the Internet that will ultimately contain more than 10,000 compounds.**

The HIV database houses chemical structures and biological data to improve the design of anti-HIV agents.

Ultimately, the database will furnish information on viral and cellular targets and help investigators monitor chemotherapy of HIV infection.

Until the entire database goes online, DAIDS has uploaded part of it at **http://www.niaid.nih.gov/daids/dtpdb/default.htm** as a pilot.

In the database, you can find anti-HIV drugs by class, including the chemical structure, chemical names, and *in vitro* activity against different HIV strains in different cell lines.

You can also view the cellular toxicity of each drug. Compounds with negative as well as positive anti-HIV activities are included.

The five sections let investigators search in various ways, for example, by the viral life cycle and targets, cellular targets, FDA-approved drugs, class, and alphabetical order.

Many agents have links to a database with drug resistance data (courtesy of International Medical Press).

DAIDS obtains the information through continuous surveillance of primary literature sources and provides literature references so users can find the original publications.

Please visit the pilot site and send your comments and suggestions to Dr. Mohamed Nasr, telephone: 301/496-0636, e-mail: mn12p@nih.gov.

## Clarification

In our last newsletter, the article "NIAID Launches Frontal Attack on Staph" stated that NIAID was supporting two new grants to sequence strains of *Staphylococcus aureus*: one to The Institute for Genome Research (TIGR) and the other to the Oklahoma University Health Sciences Center (OUHSC). While that information is correct, we mentioned TIGR's plan to release genome information but not OUHSC's.

We would like to make clear that OUHSC is also committed to a timely release of genome data.

# Staff News

**Dr. Margaret Johnston, former deputy director of the Division of AIDS, is returning to NIAID in September to head its vaccine research effort.**

In her new job, Dr. Johnston will ensure an integrated program for AIDS prevention, including vaccines and topical microbicides.

She will also act as liaison for the vaccine research community, both intramural and extramural, working closely with the AIDS Vaccine Research Committee and the NIH Office of AIDS Research.

Dr. Johnston will serve in two formal roles: associate director of the Vaccine and Prevention Research Program and assistant director for HIV/AIDS vaccines, reporting directly to Dr. Fauci in the latter role.

At Council, Dr. Fauci announced other staff changes. Ms. Sarah Carr, former head of NIAID's Office of Policy Analysis, left to work on genetic testing policy for NIH and DHHS. Dr. Jane Kinsel is now acting director of that office.

Dr. Fauci also named Dr. Stephanie James acting deputy director of the Division of Microbiology and Infectious Diseases. As previously announced, Dr. George Curlin is now acting DMID director, following the appointment of Dr. John R. La Montagne as NIAID deputy director.

# At Council, NIAID Seeks Advice on Bioterrorism

**In light of the recent move in Washington to better shield the nation from bioterrorist threats, NIAID is looking at its role of funding basic research of human pathogens that could be wielded as agents of bioterrorism.**

NIAID faces such questions as, do we have enough basic research on the organisms most likely to be used?

To gain input on this topic, Council heard a sobering presentation by Dr. Donald A. Henderson, distinguished service professor, Johns Hopkins University School of Hygiene and Public Health.

Dr. Henderson is known for his leadership of the World Health Organization's global smallpox eradication campaign.

Bioterrorism has been in the news lately in response to a growing belief by experts that it is, as Dr. Henderson told Council, "more likely than ever and far more fearsome than explosives or chemicals."

The Senate subcommittee for NIH appropriations held a hearing on June 2 on the nation's capacity to deal with bioterrorism, and the government is taking a close look at how to meet potential threats.

Several new initiatives are already under way. One for the Defense Department provides $300 million to train national guard units.

In addition, the FBI is adding new agents, and the President announced a move to stockpile vaccines and antibiotics for civilian use. As Dr. Henderson told Council, our society is ill-equipped to diagnose, characterize epidemiologically, and respond to biological weapons, whose research needs converge with those of emerging infectious diseases.

Our nation needs much better surveillance, a better network of laboratories, diagnostic tools, and properly trained health professionals.

Regarding the latter, smallpox, anthrax, and plague, the organisms considered most likely to be used, would not readily be recognized by physicians or diagnosed by laboratory tests because these infections have never been seen by practicing health professionals in the U.S.

This leaves us vulnerable to a threat Dr. Henderson described as "every bit as grim and foreboding as the picture painted of nuclear winter."

The delay to disease onset and ability of infectious organisms to spread raise enormous questions about how to protect public health, questions we are ill-prepared to answer.

For example, in a bioterrorist act involving aerosolized anthrax, people would start having symptoms three to four days after exposure to the almost universally fatal, but highly stable, spores.

By the time symptoms began to occur, it would be too late for therapy, and people would die within a matter of days.

Further, because spores can survive at least 50 years in the desiccated state, it is not known when it would be safe to reenter a contaminated area.

Anthrax cannot be spread from person to person, so smallpox, which can, presents a different scenario.

Smallpox is less stable but highly infectious. Exposed people who become ill would readily infect others while unsuspecting physicians would be slow to diagnose the disease.

Even after an epidemic was uncovered, halting further spread would be hard because of limited supplies of vaccine and a lack of an effective therapy.

## Major Bioterrorism Threats

- Anthrax
- Smallpox
- Plague
- Tularemia
- Toxins

# Novel HIV Therapies: Integrated Preclinical/Clinical Awards

**At June Council, NIAID awarded five grants and one supplement (see box below) in response to program announcement PAR 97-080, targeting the discovery, preclinical evaluation, development, and pilot clinical study of novel agents and strategies to suppress HIV replication and interfere with the consequences of infection.**

The PA solicited applications for the Integrated Preclinical/Clinical Program (IPCP), which replaces the National Cooperative Drug Discovery Groups for the Treatment of HIV Infection (NCDDG-HIV) and the Strategic Program for Innovative Research on AIDS Treatment (SPIRAT). The next application due date is November 11, 1998.

## Development of HIV Co-Receptor Inhibitors

***Michael Lederman, Case Western Reserve University***

In this new grant, Dr. Lederman and co-workers will perform exclusively preclinical research to design, synthesize, characterize, and test molecules that inhibit HIV-1 at the level of entry; AOP-RANTES is the lead molecule.

***Project 1*** Dr. Robin Offord, University of Geneva

Development of New HIV Co-Receptor Inhibitors

***Project 2*** Dr. Eric Arts, Case Western Reserve University

HIV-1 Resistance to Chemokine Analogs

***Project 3*** Dr. Donald Mosier, The Scripps Research Institute

Activity of HIV Co-Receptor Antagonists in hu-PBL-SCID Mice

## Antigen Delivery for Adjuvant HIV Immunotherapy

***Charles Rinaldo, University of Pittsburgh***

The investigators will use therapeutic vaccination in the context of HAART therapy to restore HIV-specific T-cell reactivity. In this new grant, two approaches will be used in preclinical systems: dendritic cell-based immunotherapy and DNA immunization. Pilot clinical studies will test the ability of HIV-1 antigen- and cytokine-expressing autologous dendritic cells to improve HIV-specific immune responses in infected people. An SIV model will test feasibility and proof-of-concept before the PIs begin clinical studies, highlighting a strength of this program in coordinating preclinical and clinical research.

***Project 1*** Dr. Simon Barratt-Boyes, University of Pittsburgh

Dendritic Cell-Based Adjuvant Therapy for HIV: SIV Model

***Project 2*** Dr. Louis Falo, University of Pittsburgh

Adjuvant HIV Immunotherapy: DNA-Based Immunization

***Project 3*** Dr. Albert Donnenberg, University of Pittsburgh

Direct Measurement of T-Cell Turnover in SIV Infection Following Pharmacological and Therapeutic Intervention

***Project 4*** Dr. Cara Wilson, University of Colorado

Dendritic Cell Therapy for HIV: Role of Cytokines on Enhanced T Cell Function

***Project 5*** Dr. Michael Lotze, University of Pittsburgh

Dendritic Cell Therapy for HIV: Pilot Clinical Study

*Continued on next page*

## Therapy of HIV with Genetically Modified T-Cell Clones

***Philip Greenberg, Fred Hutchinson Cancer Research Center***

Performing both preclinical and pilot clinical studies, the investigators of this renewal SPIRAT grant are developing and testing strategies for establishing an effective T-cell response to HIV-1. They will accomplish this by using adoptive transfer of autologous, HIV-specific CD8+ and CD4+ T-cell clones and will monitor the effects on virus reservoirs and viral diversity.

***Project 1*** Dr. Stanley Riddell, FHCRC

Treatment of HIV with Gene-Modified CD8+ T-Cell Clones

***Project 2*** Dr. Philip Greenberg, FHCRC

Transfer of HIV-Specific CD4+ T-Cell Clones with Genes Inhibiting HIV

***Project 3*** Dr. James Mullins, University of Washington

Impact of T-Cell Therapy on HIV Population Dynamics

## Combination Genetic and Immune Therapies for AIDS

***Gary Nabel, University of Michigan***

Dr. Nabel's lab will use molecular genetic and other strategies to inhibit viral replication and optimize immune function in HIV-infected children and adults. For this renewal SPIRAT grant, the group continues to study the RevM10 antiviral gene and develop new antiviral vectors targeting virus and host factors, including chemokine receptors. New emphases are the transduction of hematopoietic stem cells, in addition to mature T cells, in clinical studies and the analysis of immune responses to vectors and recombinant genes in transduced cells.

***Project 1*** Dr. Gary Nabel, University of Michigan

Combination Gene Transfer, Antiviral Treatment, and Immunostimulation for HIV Infection

***Project 2*** Dr. Donald Kohn

Children's Hospital, Los Angeles

Hematopoietic Stem Cells for Gene Therapy with RevM10

***Project 3*** Dr. Garry Nolan, Stanford University

Safe Lentiviral Vectors for Gene Transfer to Non-dividing Cells

***Project 4*** Dr. Daniel Littman, New York University

Chemokine Receptor Intervention Using Gene Therapy and Animal Models

## Novel HIV Therapies: IPCP

***Ellis Reinherz, Dana-Farber Cancer Institute***

In this second renewal, the investigators will continue studying the structural biology of CD4-HIV-1 envelope interaction as a basis for rational drug discovery. This work follows their elucidation of the atomic structure of two-domain CD4 under the original grant and identification of CD4 amino acid residues that are binding sites in CD4-gp120 and CD4-MHC class II interactions. The new proposal will use x-ray crystallography and nuclear magnetic resonance to search for peptides that interfere with CD4-gp120 binding.

***Project 1*** Dr. Ellis Reinherz, Dana-Farber Cancer Institute

Structural Analysis of CD4-Ligand Interaction

***Project 2*** Dr. Stephen Harrison, Children's Hospital, Boston

Structural Biology of HIV Envelope Interactions

***Project 3*** Dr. Gerhard Wagner, Harvard Medical School

NMR-Based Discovery of HIV Inhibitors

**Novel HIV Therapies**—*continued on page 19*

*FEATURE article*

# Speeding Up Grant Awards: The Next Step

**NIAID is narrowing the gap between application receipt and award dates by as much as 75 percent, offering an approach that would benefit both NIH and its extramural research community.**

A new hyperaccelerated review process will cut receipt to award time to about three months (see timeline below) from the NIH norm of one year, while maintaining or even enhancing the quality of peer review. It builds on our creation and implementation of electronic initial and Council review systems, which NIAID has licensed to other NIH organizations (see box at upper right of next page).

Following the successful collaboration of NIAID and CSR's Tropical Medicine and Parasitology (TMP) study section (see last newsletter issue), the pair are now working on two new steps:

- a request for applications (RFA) called Hyperaccelerated Award/Mechanisms in Immune Disease Trials
- an accelerated approach for the eight new AIDS study sections

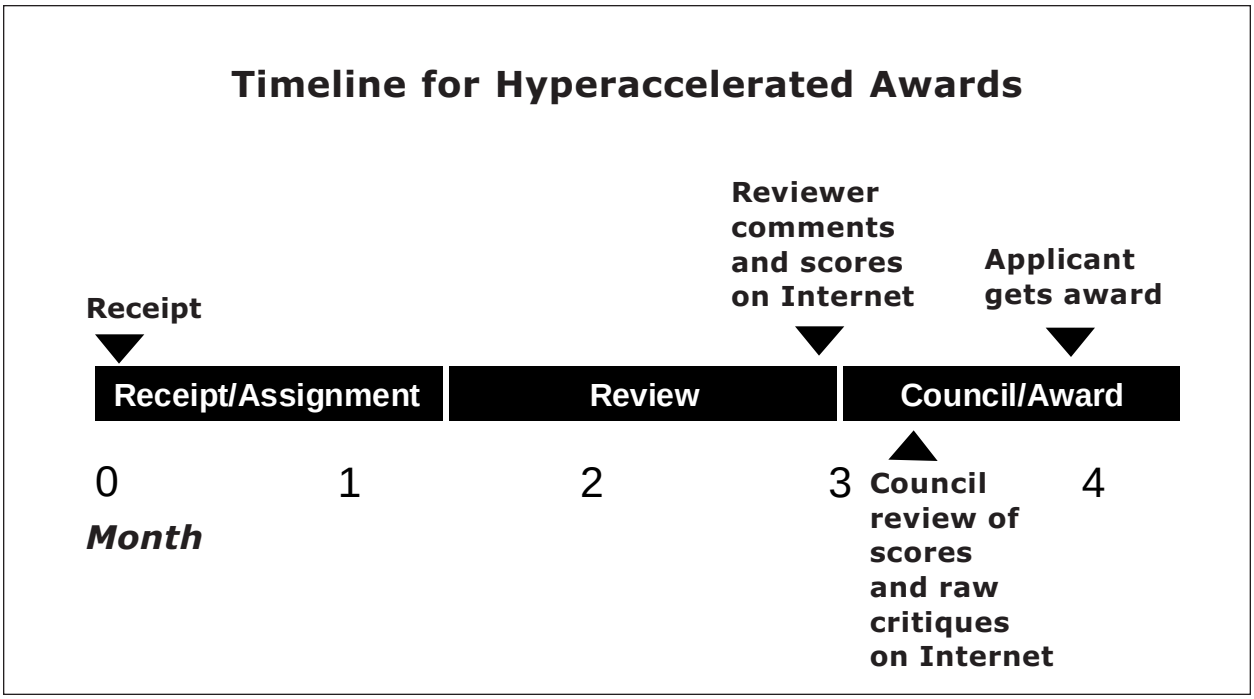
## *Hyperaccelerated RFA*

Published in May, the RFA features monthly receipt dates, applicant self-referral to NIAID, and a new study section that will be specially trained in the new system.

It takes a big step forward from the TMP work by cutting target time to funding from five months to 13 weeks from application to receipt.

The move to use these innovations stems in part from feedback from workshop and focus group participants, who highlighted the importance of studying mechanisms of interventions and disease.

Industry-supported clinical trials often omit evaluating immunologic and other parameters in patient samples. With the RFA, NIAID is striving to make awards more compatible with timelines of indus-



try-supported clinical trials in this key scientific area.

To make the award process as timely as possible, reviewers will use NIAID's electronic initial review system to review applications and enter critiques and scores into a secure Web server.

At about the seventh week of the process, SRG members will gain access to each other's reviews and view each other's comments online.

Then, the application will be discussed and voted on during a monthly conference call.

Within the next two weeks, summary statements will be ready, and all other administrative requirements will be completed during weeks 10 to 13.

At that point, applicants in the fundable range will send NIH all necessary materials, expedited Council review will take place, and the Institute will make the awards.

You can find the RFA on the Web at **http://www.nih.gov/grants/guide/rfa-files/RFA-AI-98-006.html**.

### *Wide NIH interest*

With its electronic review systems in place, NIAID is already beginning to recruit SRG members.

Institutes that do not have expedited Council review are developing procedures to do so.

The initiative is being cosponsored by the National Heart, Lung, and Blood Institute; National Institute of Arthritis and Musculoskeletal and Skin Diseases; National Institute of Diabetes and Digestive and Kidney Diseases; National Institute of Neurological Disorders and Stroke; and the NIH Office of Research on Women's Health.

NIAID expects to finish testing the electronic review site, train reviewers, assist basic researcher-industry collaborations, and work with applicants by September; the first applications are scheduled to arrive in October for awards in January 1999.

This fall, CSR's AIDS study sections will be using the basic features of the TMP electronic peer review trial.

We will provide more information on that effort in the September issue of this newsletter.

## NIAID's Electronic Initial Review System NIH-Wide

| | |
|---|---|
| NIDR | 53 Events |
| NIAID | 24 Events |
| NIGMS | 2 Events |
| NIDCD | 5 Events |
| NCI | 5 Events |
| CSR/TMP | 7 Events |

**To Come:**

AIDS Study Sections in CSR

Hyperaccelerated Review (CSR, NIAID, NIAMS, NIDDK, NINDS, NHLBI, and ORWH)

## Hyperaccelerated Review RFA—Key Features

**Application page limit—**10 pages plus references for the science portion.

**IRB approval of mechanistic studies and core trial—**required for award but not application.

**Agreement of PI and sponsor of core clinical trial—**required of applicant and institution.

**Support levels—**Limited to $160,000 per year for direct costs except by permission.

**Types of projects—**Both pilot or feasibility and definitive projects will be eligible.

**Amended applications—**By invitation only (limited to those with minor problems; will be reviewed and voted on at next monthly conference call).

**Vaccine Meeting—**
*continued from page 11*

Called FluMist, the vaccine not only produces antibody but also mucosal immunity in the nose.

It was developed through a collaboration joining NIAID intramural labs, researchers at the University of Michigan School of Public Health, and biotech company Aviron, including clinical testing at six sites of NIAID's Vaccine and Treatment Evaluation Units and four clinical sites funded by Aviron.

In a recent efficacy trial, the vaccine prevented 93 percent of flu infections in children under five years of age; 288 children received one dose of vaccine (using the same strains as the traditional influenza vaccine) or placebo; 1,314 children received two doses 60 days apart.

Both regimens were safe, and the vaccine prevented infection from both flu strains prevalent at the time, influenza A (H3N2) and B. The spray was well tolerated and accepted.

These results were published in the May 14 *New England Journal of Medicine.*

The symposium was sponsored by Merck, BIO Council of Biotechnology Centers, and NIAID.

Held in New York, it was part of BIO 98, sponsored by the Biotechnology Industry Organization.

**NIH news—**
*continued from page 9*

# New NIH Guidelines for Conference Grants

**In May, NIH announced updated guidelines for conference grants, including some specific to NIAID.**

The Institute supports conference grants on a wide range of topics relevant to its research mission. Applications must meet certain criteria to be considered (see box at right).

For more information, contact:

*DAIT—Dr. Lawrence Prograis*
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*301/496-7291*
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## Conference Grant Guides

Cost at least $2,500

Apply at least six months before the meeting

Applications reviewed at regular (R01) receipt dates

Applications also accepted throughout the year with prior Institute approval

Usually awarded as a cooperative agreement

**Novel HIV Therapies**—*continued from page 16*

### Ribozyme Gene Therapy and Stem Cell Transplantation for AIDS Lymphomas

***John Zaia, City of Hope National Medical Center***

This is a supplement to an existing project that has shown the safety of infusing genetically engineered, autologous CD34+ peripheral blood progenitor cells in HIV-infected persons.

New work centers on a phase I/IIA gene therapy study using a double ribozyme targeting *tat* and *rev* in AIDS patients with non-Hodgkin's lymphoma. The PI will test whether genetically altered cells can engraft and express the transgene after total marrow ablation.

**Modular Grants**—
*continued from page 5*

and less of a regulatory mode.

Both NIAID and the National Heart, Lung, and Blood Institute have successfully used modular grants.

For the past two years, NIAID has been awarding them for the Innovation Grant Program for HIV Vaccine Research.

Study sections like the approach because it keeps the review discussion focused more on science and less on budget.

For more on modular grants, go to the September 1997 *Council News* newsletter article, online at **http://www.niaid.nih.gov/ncn/nl0597/page2.htm** and scroll down to the article.


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